

# Mycophenolate Mofetil Therapy in Taiwanese Myasthenia Gravis

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## Abstract-

**Background:** Mycophenolate mofetil (MM) has been successfully used for the treatment of immune-mediated diseases, including myasthenia gravis (MG). We compare our experience treating Taiwanese myasthenic patients with MM to analogous Caucasian series

**Methods:** From October 2003 to April 2008, we treated 6 myasthenic patients with MM for at least one year at Shin Kong Wu Ho-Su Memorial Hospital. The inclusion criteria for MM treatment included poor responses to previous treatment or intolerance to the side effects of previous immunosuppressive therapies. The MM was given orally with a dose of 1 g twice per day. Mandatory surveillance laboratory studies and clinical assessment were performed periodically.

**Results:** Three of our six patients responded well to MM treatment in terms of improvement in MG score and achievement of minimal manifestation status. The fourth patient showed delayed onset of response 12 months after commencement of MM treatment. Steroid-sparing effect could be demonstrated in 4 patients. The overall response rate (66%) was slightly lower than that reported for Caucasian series. Clinical improvement generally began in the second to four months. MM was well tolerated.

**Conclusion:** MM was well tolerated by our six treated patients. Although the clinical response was modest, MM has its advantage of a relatively rapid response onset and steroid-sparing effect.

**Key Words:** Immunosuppression, Myasthenia gravis, Mycophenolate mofetil

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## INTRODUCTION

Because of its potent immunosuppression, mycophenolate mofetil (MM) has been used for treatment of various immune-mediated diseases<sup>(1)</sup> including myasthenia gravis (MG)<sup>(2)</sup>. In an open-label study conducted by Ciafaloni et al., eight out of 12 patients with

refractory MG improved after MM treatment<sup>(3)</sup>. Chaudry et al.<sup>(4)</sup>, reported improved functional status in 19 of 32 MG patients receiving MM, with the lowering of the steroid dosage in 16 patients. However, there are few reports of MM treatment in Asian MG patients<sup>(5)</sup>. Given the possibility of ethnic differences between Taiwanese and Caucasian MG patients<sup>(6)</sup>, we present our experience

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in treating six Taiwanese MG patients with MM and compare it to analogous Caucasian series.

## MATERIALS AND METHODS

### Patient characteristics

From October 2003 to April 2008, six female MG patients (age 34-54 years) received MM treatment for at least 1 year at Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan. The diagnosis of MG was based on clinical, pharmacological, serological and electrodiagnostic criteria. Four patients (cases 2, 3, 4 and 5) were positive for acetylcholine receptor antibody (AChRAb), and one (case 6) positive for muscle-specific kinase antibody (MuSKAb). All of the patients were affected by generalized MG with Osserman's classifications of group IIa (n = 4), IIb (n = 1) or III (n = 1) (Table 1). The duration of illness ranged from 5 to 12 years. The inclusion criteria for MM treatment included poor responses to previous therapies for all cases or intolerable side effects related to previous immunosuppression (case 3 and 5). All patients received anti-cholinesterase therapy; two were also treated with prednisolone, and two receiving combined prednisolone and azathioprine therapy. Five patients had undergone thymectomy, with the thymic pathology consisting of thymic hyperplasia (n = 4) and thymoma (n = 1). All patients gave informed consents for MM treatment prior to their inclusion in the study.

### Mycophenolate mofetil treatment

The MM was given orally (1 g twice a day). Laboratory studies, including complete blood cells with

differential count, liver and renal function tests, were performed at baseline and months 1, 2, 3, 6, 9 and 12.

### Clinical and laboratory evaluation

Clinical status was evaluated using modified MG score<sup>(7)</sup>. The primary measure of response to treatment was the MGFA post-intervention status scale. Complete remission was reserved for absence of myasthenic symptoms or signs for at least 1 year and no therapy for MG during that time. Minimal manifestation was defined as no symptoms or functional limitations from MG but with some weakness on examination of some muscles. MG scores and AChRAb concentrations were measured at baseline and yearly thereafter. The AChRAb and MuSKAb levels were detected using standard radioimmunoprecipitation kits (RSR Limited, Cardiff, UK).

## RESULTS

### Case 1

The 35-year-old female patient with mixed connective tissue disease first presented with fever, alopecia, photophobia, oral ulcers, chest tightness, arthritis and myalgia in 1989. In 1995, ptosis, dysphagia and generalized weakness with diurnal fluctuation developed and MG was diagnosed. Her electrophysiologic studies and serum AChRAb were negative. Despite aggressive immunotherapy with cyclosporine (200 mg/day), azathioprine (75 mg/day) and prednisolone (20 mg/day) for 6 months, her myasthenic weakness did not improve. Plasmapheresis was performed intermittently for episodes of acute deterioration. In April 2004, MM ther-

**Table 1.** Baseline characteristics of six female patients with refractory myasthenic gravis (MG) receiving mycophenolate mofetil treatment

No.	Age	Thymic pathology	Clinical grade <sup>a</sup>	MG score	AChRAb <sup>b</sup> (nmole/l)	Duration of MG (year)	Immunosuppressants (mg/d)	
							Prednisolone	Azathioprine
1	37	No operation	IIb	6	—	12	20	50
2	39	Hyperplasia	IIa	6	321.7	7	0	0
3	54	Hyperplasia	IIa	8	89.0	12	20	0
4	53	Hyperplasia	IIa	4	512.6	11	10	50
5	52	Thymoma	IIa	7	356.1	9	0	0
6	38	Hyperplasia	III	15	—	5	40	0

<sup>a</sup> Osserman's classification. <sup>b</sup> acetylcholine receptor antibody.

apy was commenced and the clinical weakness stabilized after 2 months, with her MG score decreasing from 6 (at baseline) to 2. Concomitant prednisolone (20 mg/day) was successfully tapered 14 months after MM treatment. Due to progressive hair loss, MM was tapered off at 20 months after MM treatment without flare-up of weakness. She reported transient somnolence during the first 2 weeks of therapy.

### Case 2

The 36-year-old lady had suffered progressive generalized weakness since 1998. She could not tolerate the side effects associated with corticosteroids (30 mg/day). Azathioprine had been used since April, 2000 and leukopenia limited the azathioprine dosage. She underwent thymectomy for a hyperplastic thymus 2 years after the onset of disease. In October 2004, she was again admitted for plasmapheresis and MM treatment because of profound weakness. The weakness improved dramatically with a drop in the MG score from 6 at baseline to 1 after the combined treatment. Weakness recurred 10 weeks afterwards because of an incident upper respiratory infection. With a new course of plasmapheresis treatment, her clinical status stabilized 2 weeks later. Minimal manifestation was achieved 6 months after treatment, with the AchRAb titer declining slowly in parallel with the clinical MG score. After 12 months of treatment, it had dropped to approximately half of baseline (from 321.7 to 158.9 nmol/l). Currently, she remained in the minimal manifestation status at the 44 months after MM treatment with a reduced dosage of MM (1250 mg/day).

### Case 3

The 54-year-old woman presented with fluctuating ptosis and generalized weakness in 1995. Her weakness did not respond well to prolonged corticosteroid (50 mg/day) and azathioprine (100 mg/day) for over 8 months. Furthermore, diabetes mellitus and osteoporosis developed and were assumed to be the direct complications of corticosteroid. She could not tolerate the side effects associated with corticosteroids, and leukopenia limited the azathioprine dosage. Thymectomy for a

hyperplastic thymus was done in 1999. She was admitted for plasmapheresis due to profound weakness three times in 2000, 2003, and 2005. She had started the MM treatment (2000 mg/day) since May 2007. Initial dizziness and somnolence was noted. The weakness improved gradually with a drop in the MG score from 8 at baseline to 6 after 4 months of the MM treatment. Minimal manifestation had been achieved after 11 months of treatment. Prednisolone was then smoothly tapered off and the dosage of MM was reduced to 1250 mg per day.

### Case 4

The 53-year-old female patient was diagnosed as MG for fluctuating diplopia and generalized weakness in 1997. Although transcervical thymectomy for a hyperplastic thymus was successfully performed in 2000, her weakness had been inadequately controlled by combined prednisolone (60 mg/day) and azathioprine (100 mg/day) treatment. Periodic plasmapheresis was needed for acute worsening at the interval of three to six months. The dosage of prednisolone was reduced to 10 mg per day due to the occurrence of peptic ulcer bleeding in 2005. We started the MM treatment in May 2006. In the first year of MM treatment, general weakness did not improve well and three courses of plasmapheresis were needed for clinical deterioration. Fortunately, the clinical status had become stabilized after the last course of plasmapheresis in April 2007 with her MG score maintaining around 1 to 2. Concomitant azathioprine was discontinued 1 month after the starting of MM therapy and prednisolone was successfully tapered 3 months later. During the 2-year treatment of MM, no biochemical or haematological abnormalities were found.

### Case 5

The 49-year-old female patient first presented with ptosis at the age of 40 years, just 5 years after previous thymectomy for thymoma. General weakness developed rapidly 1 month after the onset of ocular symptoms. Bulbar and general weakness did not respond well to corticosteroid treatment. Severe leukopenia developed with azathioprine treatment (100 mg/day) necessitating

intermittent plasmapheresis for amelioration of symptoms. At commencement of MM treatment in October 2003, her MG score was 7. During the 13-month treatment, the MG score fluctuated around 7, without dramatic clinical improvement. She experienced a hypoxic episode secondary to accidental aspiration 13 months after conclusion of MM treatment.

### Case 6

The 35-year-old female patient was diagnosed with ocular MG in February 2002. She was positive for MuSKAb. Thymectomy for a hyperplastic thymus was performed 2 months after the diagnosis. Generalized weakness and respiratory failure developed 1 month after the operation, necessitating intermittent plasmapheresis for the relief of her respiratory crisis. High-dose prednisolone (1 mg/kg/day) and azathioprine (100 mg/day) could not halt weakness progression, however. The combined MM and prednisolone treatment was commenced in October 2004. The weakness continued to fluctuate during the 19 months of MM treatment. Therefore, we replaced MM with tacrolimus.

## DISCUSSION

Three of our six patients (case 1 to 3) responded well to MM treatment in terms of improvement in MG score and achievement of minimal manifestation status (Table 2). The case 4 also showed improvement of MG weakness, but with a delayed response to MM treatment 12 months after. Steroid-sparing effect could be demonstrat-

ed in 4 patients and azathioprine was discontinued for all 2 users. The overall response rate (66%) was slightly lower than that reported for Caucasian analogs<sup>(3,4)</sup>. In contrast, case 5 and case 6 developed several episodes of respiratory crisis necessitated ventilatory support. Both of them did not respond to MM treatment. Meriggioli<sup>(8)</sup> also reported that five of 13 MG patients who suffered a respiratory crisis did not improve with MM treatment. Therefore, respiratory involvement may be a predictor of poor prognosis with MM treatment. Longer myasthenia duration and shorter MM treatment were reported to be associated with a less favourable response<sup>(4)</sup>. In our series, however, the most rapid response to MM was associated with the longest history of MG (case 1 and 3). Further, the patient with MG of shortest duration had a poorest response (case 6). Thus, disease duration was not a major determinant of MM responsiveness in our Taiwanese MG patients.

In the study of Meriggioli et al., the mean time to first objective improvement was 10.8 weeks (range 4-40), with onset of improvement occurring 8 weeks or less after commencement of therapy in 33 of 62 responders (53%)<sup>(8)</sup>. Ciafaloni et al., reported improvement at between 2 weeks and 2 months after MM initiation in all eight patients<sup>(3)</sup>. The onset of clinical improvement in our study occurred at 2 to 4 months for the 3 good responders. These findings are similar to the results of previous studies, and confirm the relatively faster onset of therapeutic effect comparing MM to conventional immunosuppressants<sup>(1)</sup>.

All our patients tolerated MM well. Diarrhea, the

**Table 2.** Clinical status of six female patients with refractory myasthenic gravis (MG) receiving mycophenolate mofetil treatment for 1 year

No.	Clinical grade <sup>a</sup>	MG score	AchRAB <sup>b</sup> titer	Post-intervention status	Onset of improvement	Immunosuppressants (mg/d)	
						Prednisolone	MM
1	Ila	2	—	Minimal manifestation	2 months	10	1500
2	Ila	1	158.9	Minimal manifestation	3 months	0	1250
3	Ila	1	65.0	Minimal manifestation	4 months	0	1250
4	Ila	2	510.6	Improved	12 months	0	1750
5	Ila	7	300.7	Unchanged	—	0	2000
6	III	13	—	Unchanged	—	50	2000

<sup>a</sup> Osserman's classification. <sup>b</sup> acetylcholine receptor antibody.

most commonly reported side effect, did not occur. However, three patients experienced transient somnolence during the initial 1-2 weeks of MM treatment. We suggest this might be the result of slower metabolism during the initial treatment period with high dosage of MM. A more gradual titration program may reduce the occurrence of this side effect. There was no alteration of hemogram or serum biochemistry.

Azathioprine is the most widely used immunosuppressant for the treatment of MG. However, delayed clinical response is often noted<sup>(9)</sup>. During the past 2 decades, newer immunosuppressants have been developed and applied successfully in the treatment of MG, including cyclosporine, cyclophosphamide, tacrolimus and MM<sup>(9)</sup>. The clinical efficacy of cyclosporine in MG was first suggested by a small, randomized, placebo-controlled study, which has not been followed by similar studies on larger groups of patients<sup>(10)</sup>. Side effects of hypertension and nephrotoxicity are common with cyclosporine, and clinical experience suggests the drug is less well tolerated than either azathioprine or MM<sup>(11)</sup>. Based on the potential concern about nephrotoxicity of cyclosporine, we chose the MM as the alternative treatment in this series of refractory MG patients.

In conclusion, MM was well tolerated by our MG patients. Although the clinical response was modest, MM has its advantage of a relatively rapid response onset and steroid-sparing effect.

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